REMARKS

Claims 1-16, 18-25 and 49 were pending in the subject application. Applicant herein above has amended claim 1 and 49, canceled claims 3 and 4 without prejudice, and added new claims 50 and 51. Accordingly, claims 1, 2, 5-16, 18-25, 49 and 50-51 are presented for the Examiner's consideration.

Support for new claims 50 and 51 may be found, *inter alia*, on page 27, lines 16-17 of the subject application.

Rejection under 35 U.S.C. § 112, first paragraph
Written Description

On pages 2-4 of the January 16, 2003 Office Action, the Examiner rejected claims 1, 3-15, 18-25, and 49 under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Examiner stated that applicant's arguments filed July 8, 2002 have been fully considered but they are not persuasive. The Examiner maintained that the evidence of record has not described any variant sequences of the nucleotide sequence set forth in SEQ ID NO:1 embraced by the claims (for clarity, variants include those nucleotide sequences that share [87% or 95%] homology with the nucleotide sequence set forth in SEQ ID NO: 1 and those sequences that hybridize to the nucleotide sequences set forth in SEQ ID NO: 1). The Examiner stated that possession may be shown by reduction of practice or by describing the relevant identifying characteristics of the claimed nucleotide sequences. The Examiner noted that the

specification discloses isolation of a nucleotide sequence (SEQ ID NO: 1) that is a novel human ABC promoter, but alleged that it does not disclose other mammalian ABC promoters or human ABC promoters or other ABC promoters from other cell types. The Examiner also alleged that there is no evidence on the record of a relationship between the structure of any ABC promoter and the claimed human ABC promoter that would provide any reliable information about the structure of other ABC promoters within the genus; that there is no evidence on the record that the claimed human ABC promoter as set forth in SEQ ID NO: 1 had a known structural relationship to any other ABC promoter sequences or the variant nucleotide sequences embraced by the claims - the specification discloses only a single human ABC promoter; and that there is no evidence of record that would indicate that any of the claimed variants of SEQ ID NO: 1, even have the biological activity of the claimed human ABC promoter set forth in SEQ ID NO: 1. In view of the above allegations, the Examiner alleged that one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because a human ABC promoter sequence is not representative of the claimed genus.

In response, without conceding the correctness of the Examiner's position but solely to advance the prosecution of the subject application, the applicant has amended claims 1 and 49 and canceled claims 3 and 4. As amended, claims 1 and 49 overcome the Examiner's stated grounds for rejection.

Claims 5-16, and 17-25 all depend directly or indirectly on claim 1, and, thus, are also in compliance with the written description requirement.

Accordingly, applicant's amended claims meet the written description requirement of 35 U.S.C. 112, and this rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph
Enablement

On pages 4-8 of the January 16, 2003 Office Action, the Examiner rejected claims 10-16 and 18-25 and 49 under 35 U.S.C. § 112, first paragraph, alleging that the specification, while being enabling for the nucleotide sequence set forth in SEQ ID NO: 1, a host cell transformed *in vitro* with a recombinant expression construct comprising the nucleotide sequence set forth in SEQ ID NO: 1 operably linked to a foreign nucleotide sequence encoding a polypeptide of interest, and an *in vitro* method of expressing foreign DNA in a host cell using the same recombinant expression construct, does not reasonably provide enablement for variants of the nucleotide sequence set forth in SEQ ID NO: 1, host cells transformed *in vivo*, and methods of transforming host cells *in vivo*. The Examiner alleged that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner stated that applicant's arguments filed July 8, 2002 have been fully considered but they are not persuasive. The Examiner maintained that host cells transformed *in vivo* and methods of transforming host cells *in vivo* are encompassed within the field of gene therapy, which was unpredictable at the time the claimed invention was filed and has remained

unpredictable thereafter. The skilled artisan could not rely on the state of the gene therapy art for practicing the invention as claimed due to the unpredictable nature of expressing a heterologous nucleotide in a host cell *in vivo*. It is maintained that the instant specification has failed to provide teachings, guidance, or working examples that would allow the skilled artisan to transform and express a foreign DNA sequence in a host cell *in vivo*. The Examiner further maintained that the evidence of record has failed to teach how to target cells in vivo, the mode of administration of an expression construct, the level of expression of a heterologous nucleotide sequence necessary to provide therapeutic benefit, and the fate of the expressed heterologous protein *in vivo*, referring to pages 6-7 of the Office action mailed January 3, 2002. The Examiner alleged that the unpredictability of the gene therapy art is discussed in Verma el and Anderson et al, which support the Examiner's arguments (above), referring to pages 7-8 of the Office Action mailed on January 3, 2002. The Examiner alleged that evidence of record has not provided adequate guidance to overcome the unpredictability of the gene therapy art as discussed by Verma and Anderson.

The Examiner proceeded to explain the basis for asserting that the variant nucleotide sequences were not enabled. The Examiner alleged that the specification has not taught any nucleotide sequences having at least 87% or 95% identity to SEQ ID NO: 1 or any nucleotide sequences that hybridize to the nucleotide sequence set forth in SEQ ID NO: 1 (termed variants hereafter) that function as an ABC promoter. The Examiner then alleged that the skilled artisan would not be able to

predict the structure of a variant that is biologically active because the specification has not provided any information as to the structural elements required for a variant to be biologically active. The Examiner also alleged that the specification does not provide any information on what nucleotides are necessary and sufficient for biological activity, e.g. which insertions, deletions and substitutions, would be permissible in a variant nucleotide sequence that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity of the sequence. The Examiner alleged that since there are no examples of a variant known to have structural homology with SEQ ID NO: 1, it is not possible to even guess at the nucleotides which are critical to its structure or function based on sequence conservation. Furthermore, the Examiner alleged that it is known in the art that nucleotide substitutions can adversely affect biological activity if nucleotides that are critical for such functions are substituted; that even a single base substitution can affect the ability of a nucleotide sequence to function as a promoter. The Examiner cited Huang et al (PNAS, 1998, 95: 14669-14674) in support this observation, and alleged Huang et al report that a single base mutation in the ζ-globin promoter repressed transcription of the human ζ-globin gene in a transgenic mouse study, referring to abstract and pages 14669, and 14672. Consequently, the Examiner alleged that excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives to obtain biologically active variant transcriptional regulatory sequence with a nucleotide sequence differing from SEQ ID NO: 1 since the nucleotide sequence of

such variants could not be predicted.

In response, without conceding the correctness of the Examiner's position but solely to advance the prosecution of the subject application, the applicant has amended claims 1 and 49 and canceled claims 3 and 4. As amended, claims 1 and 49 overcome the Examiners stated rounds for rejection.

With respect to *in vivo* transformation of cells, applicant respectfully concedes to some confusion. As applicant has pointed out in the last response, preparation of recombinant expression constructs, inserting them into living cells, and expressing the constructs in living cells has been known to those skilled in the art for at least twenty (20) years prior to the filing of the subject application. For example, in 1977, Wigler, M., et al., Cell 11: 223-232 (1977) described transformation of eucaryotic cells, specifically mammalian cells, with foreign DNA coding for a selectable phenotype. Over the years, a number of techniques have been developed for introducing DNA into mammalian cells, e.g. calcium phosphate co-precipitation, DEAE-dextron, microinjection, protoplast fusion, electroporation, lipofection, etc. Therefore, to the extent applicant's claims read on transformation of living cell, the claims are enabled. Furthermore, after making transformed mammalian cells, it is hardly difficult to insert such transformed cell back into the mammal. Indeed, numerous cancer researchers use xenographting to study development of tumors. Thus, applicant finds the Examiner's position unclear in view of this large body of prior art showing *in vivo* transformation of cells, particularly now that applicant has amended the claims to recite specific promoter sequences.

Therefore, the applicant respectfully submits that the amended claims meet the requirements of 35 U.S.C. § 112, first paragraph, and this rejection should be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

On page 8 of the January 16, 2003 Office Action, the Examiner rejected claim 49 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleged that claim 49 recites an isolated human ABC 1 gene comprising at least six exons and a promoter. The Examiner further alleged that the specification described the ABC 1 gene to span a minimum of 70KB and to contain at least 49 exons. The Examiner alleged that the ABC 1 gene as defined by the claim as amended is not consistent with the definition provided by the specification.

In response, the Applicant has amended claim 49 to clarify Applicant's invention without conceding the correctness of the Examiner's position but solely to advance prosecution of the subject application.

In view of the above mentioned amendments and remarks, the Applicant requests that the Examiner reconsider and withdraw the rejections set forth in the January 16, 2003 Office Action.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Gary J. Gershik 4/16/03
John P. White Date
Reg. No. 28,678
Gary J. Gershik
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Attachment A

(Marked-up Claims to show amendments)

1. (Amended) An isolated human *ABC1* promoter that directs transcription of a heterologous coding sequence positioned downstream therefrom, wherein the promoter is selected from the group consisting of:

   (a) a promoter comprising nucleotides having the nucleotide sequence shown in SEQ ID NO: 1; and

   (b) a promoter comprising nucleotides having the nucleotide sequence beginning at bp -469 and ending at bp +101 of SEQ ID NO: 1; ~~and~~

   ~~(c) a promoter comprising nucleotides having the nucleotide sequence that hybridizes to a sequence complementary to the promoter of (a) or (b) in a Southern hybridization reaction performed under stringent conditions.~~

2. The promoter of claim 1, wherein the promoter comprises the nucleotide sequence shown in SEQ ID NO: 1.

~~3. The promoter of claim 1, wherein the promoter comprises a nucleotide sequence that is at least 87% homologous to SEQ ID NO: 1.~~

~~4. The promoter of claim 3, wherein the promoter comprises a nucleotide sequence that is at least 95% homologous to SEQ ID NO: 1.~~

5. A recombinant expression construct effective in directing the transcription of a selected coding sequence which comprises:

   (a) a human *ABC1* promoter nucleotide sequence according to claim 1; and

   (b) a coding sequence operably linked to the promoter, whereby the coding sequence can be transcribed and translated in a host cell, and the promoter is heterologous to the coding sequence.

6. The recombinant expression construct of claim 5, wherein the coding sequence encodes a transporter polypeptide.

7. The recombinant expression construct of claim 6, wherein the transported polypeptide is ABCA1 transmembrane transporter protein.

8. The recombinant expression construct of claim 6, further comprising a nucleic acid segment encoding a transactivator protein that upregulates the ABC1 promoter.

9. The recombinant expression construct of claim 8, wherein the transactivator protein is the Liver-X-Receptor, the Retinoid-X-Receptor, or a heterodimer of the Liver-X-Receptor and the Retinoid-X-Receptor.

10. A host cell comprising the recombinant expression construct of claim 5.

11. The host cell of claim 10, wherein the host cell is stably transformed with the recombinant expression construct.

12. The host cell of claim 10, wherein the host cell is a macrophage.

13. The host cell of claim 10, wherein the host cell is an immortalized cell.

14. The host cell of claim 10, wherein the cell is selected from the group consisting of RAW cells, African green monkey CV-1 cells and human 293 cells.

15. A method for expressing a foreign DNA in a host cell comprising: introducing into the host cell a gene transfer vector comprising the *ABC1* promoter according to claim 1 operably linked to the foreign DNA encoding a desired polypeptide or RNA, wherein said foreign DNA is expressed.

16. The method of claim 15, wherein the promoter nucleotide sequence is identical to the sequence represented by SEQ ID NO: 1.

18. The method of claim 15, wherein the gene transfer vector encodes and expresses a reporter molecule.

19. The method of claim 18, wherein the reporter molecule is selected from the group consisting of beta-galactosidase, beta-glucuronidase, luciferase, chloramphenicol acetyltransferase, neomycin phosphotransferase, and guanine xanthine phosphoribosyltransferase.

20. The method of claim 15, wherein the introducing is carried out by adenovirus infection, liposome-mediated transfer, topical application to the cell, or microinjection.

21. The method of claim 15, further comprising introducing into the cell a gene transfer vector comprising a nucleic acid segment encoding a transactivator protein capable of upregulating the ABC1 promoter.

22. The method of claim 21, wherein the transactivator protein is the Liver-X-Receptor, the Retinoid-X-Receptor, or a heterodimer of the Liver-X-Receptor and the Retinoid-X-Receptor.

23. The method of claim 15, further comprising contacting the cell with a transactivator protein capable of upregulating the ABC1 promoter

24. The method of claim 23, wherein the transactivator protein is the Liver-X-Receptor, the Retinoid-X-Receptor, or a heterodimer of the Liver-X-Receptor and the Retinoid-X-Receptor.

25. The method of claim 24, further comprising contacting the cell with an agonist of the Liver-X-Receptor, of the Retinoid-X-Receptor, or of a heterodimer of the Liver-X-Receptor and the Retinoid-X-Receptor.

49. (2X Amended) An isolated human *ABC1* gene comprising ~~at least six exons and~~ a promoter, wherein the promoter is selected from the group consisting of:

(a) a promoter comprising nucleotides having the nucleotide sequence shown in SEQ ID NO: 1; and

(b) a promoter comprising nucleotides having the

nucleotide sequence beginning at bp -469 and ending at bp +101 of SEQ ID NO: 1~~, and~~

~~(c) a promoter comprising nucleotides having the nucleotide sequence that hybridizes to a sequence complementary to the promoter of (a) or (b) in a Southern hybridization reaction performed under stringent conditions~~.

50. (New) An isolated nucleic acid that has the nucleotide sequence beginning at bp -101 and ending at bp -32 of SEQ ID NO: 1.

51. (New) A recombinant expression construct which comprises the nucleic acid according to claim 50.